



## **New Peer Reviewed Article Describes Mechanism of Action of PLX-PAD in Ameliorating Preeclampsia and Indicates their Superiority over other cells**

- *First published study comparing therapeutic outcome of placenta-derived cells as compared to cells derived from bone marrow or fat tissue*
  - *Data describes the mechanism of action of PLX-PAD cells in preeclampsia*
  - *Study independently conducted by scientists at Texas A&M Health Science Center*
  - *PLX-PAD Cells recently received Orphan Drug Designation for Severe Preeclampsia*

**HAIFA, ISRAEL, January 6, 2016 --** [Pluristem Therapeutics Inc.](#) (NasdaqCM: PSTI , TASE: PLTR), a leading developer of placenta-based cell therapy products, today announced the publication of a scientific study of PLacental eXpanded (PLX) cells in the prominent peer-reviewed journal [Clinical Science](#). The paper, titled “Human Placenta-Derived Stromal Cells Decrease Inflammation, Placental Injury, and Blood Pressure in Hypertensive Pregnant Mice,” describes the positive findings of a recent preclinical study of PLX-PAD cells for the treatment of preeclampsia. This marks the first published study indicating the superiority of placenta-derived mesenchymal cells in a therapeutic outcome as compared to cells derived from bone marrow or fat tissue, thus having implications beyond preeclampsia. Scientists also described the potential mechanism of action by which PLX-PAD cells treated symptoms of preeclampsia. Conducted by independent scientists at the Texas A&M Health Science Center/Baylor Scott & White Health, the paper was co-authored by scientists from the Health Science Center and Pluristem Therapeutics.

Preeclampsia occurs in approximately 6-8% of pregnancies worldwide, and greatly increases the risks of serious illness and death for a pregnant woman and her baby. There is no cure other than delivery, which may be necessary even if the baby will be born prematurely, in some cases even before a viable gestational age is reached. Pluristem’s PLX-PAD cells recently received Orphan Drug Designation from the U.S. Food and Drug Administration (FDA) for the treatment of severe preeclampsia.

“This study is extremely important at this time because it provides data which demonstrate two critical outcomes. First, study findings indicated the potential mechanism of action to explain the effectiveness of PLX-PAD cells in the treatment of symptoms of preeclampsia following intramuscular injection. Second, the data have implications beyond preeclampsia by suggesting the superiority of placenta-derived cells over those sourced from fat tissue and bone marrow,” stated Pluristem Chairman and CEO Zami Aberman. “The study confirms the power of placental cells to address complex diseases without harming the patient, through a clear mechanism of action and multifactorial response. Specific to preeclampsia, with the support of the FDA’s Orphan Drug

Designation, we look forward to advancing into clinical studies in this severe unmet need that causes so many serious consequences for pregnant women and their babies.”

Data from the study showed that PLX-PAD cells, which are derived from placental cells, were able to normalize or significantly lower all the key symptoms of preeclampsia in two mouse models of the disease with only one intramuscular dose. PLX-PAD cells normalized blood pressure, marker levels of kidney function, and blood vessel function, all of which are considered to be key physiologic features contributing to preeclampsia. PLX-PAD also reduced levels of markers of inflammation and placental injury, thought to be central to the disease process as well.

Another important finding was that PLX-PAD cells did not affect healthy pregnant mice or their fetuses, consistent with prior independent studies conducted at Charles River. The trial data provide further evidence that administration of PLX cells into muscle generates a systemic effect, without any cell migration or engraftment into the mother, the placenta or her fetus. The article cites an earlier animal study, in which PLX-PAD cells were shown to stay in the muscle in which they were injected, and that they were no longer detectable after several weeks, i.e., there was no migration or engraftment of PLX cells.

The study also compared PLX-PAD cells, which are placenta derived, to cells derived from bone marrow and human adipose (fat) tissue, which were found to have no therapeutic effect. Data showed that PLX-PAD cells successfully treated symptoms that are present in diseases beyond preeclampsia, including immune system disturbances, excessive inflammation, and vascular dysfunction. Cells from bone marrow and fat tissue administered in these studies did not improve outcomes.

### **Additional Information about the Study**

There were three study arms. On gestational days 13, 15 and 17, pregnant C57BL/6J mice were given intraperitoneal injections of a control (saline), TLR3 agonist or TLR7 agonist. Administration of TLR3 or TLR7 agonists generated two parallel animal models of preeclampsia. On gestational day 14, mice within each group received an intramuscular injection of either a control (PlasmaLyte) or PLX-PAD cells. Selected groups of TLR3 and TLR7 agonist-exposed mice received either adipose cells or bone marrow cells on day 14, administered intramuscularly as well.

Mice exposed to either TLR3 or TLR7 agonists developed preeclampsia-like symptoms; these included hypertension, signs of kidney dysfunction (abnormal urinary protein/creatinine ratio), and signs of vascular dysfunction (abnormal endothelium-dependent relaxation responses). Those treated with intramuscular injection of PLX-PAD cells on day 14 of gestation exhibited significantly decreased systolic blood pressure by day 17. In both mouse models of preeclampsia, each decrease was statistically significant ( $p < 0.05$ ) for PLX-PAD treated mice as compared to control. By day 17, PLX-PAD treatment normalized the elevated levels of urinary protein/creatinine ratio in both models, and both decreases were statistically significant ( $p < .05$ ) as compared to control. On gestational day 17, aortic endothelium-dependent relaxation responses improved significantly in PLX-PAD treated mice both in the TLR3 and the TLR7 models of preeclampsia, and the improvements were statistically significant for both ( $p < .05$ ) as compared to

control. Treatment with PLX-PAD cells also reduced the levels of markers of systemic inflammation and placental injury in these models.

In both mouse models of preeclampsia, single doses of PLX-PAD cells were able to reduce all of the measured preeclampsia symptoms in these mice. In contrast, human adipose or bone marrow cells were not able to reduce the inflammation, hypertension, or proteinuria in these preeclamptic mice.

The cells were shown to secrete multiple chemical factors thought to address pathological processes central to the disease, including hMMP-1, hMMP-2, hMMP-3, and hTIMP-1. Also observed in treated mice were increased levels of mEGF and mVEGF. These findings suggest that PLX-PAD cells exert multifactorial therapeutic mechanism to address various features of a complex disease process.

### **About Preeclampsia**

Preeclampsia is one of the most common medical complications of pregnancy, and one of the leading known causes of premature births, stillbirths and early neonatal and maternal deaths. The disease occurs after the 20th week of pregnancy, and is characterized by high blood pressure and significant amounts of protein in the urine or end-organ dysfunction. The disease may lead to liver and renal failure, central nervous system (CNS) abnormalities including seizures, and disseminated intravascular coagulopathy. The only definitive treatment for preeclampsia is delivery. Severe preeclampsia, which occurs in 1% of pregnancies in the U.S., is defined by the presence of at least one additional symptom in a patient meeting the criteria for preeclampsia; these additional symptoms include severe high blood pressure, signs of severe kidney malfunction, low platelets, persistent headaches, and pulmonary edema.

### **About Pluristem Therapeutics**

Pluristem Therapeutics Inc. is a leading developer of placenta-based cell therapy products. The Company has reported robust clinical trial data in multiple indications for its patented PLX (PLacental eXpanded) cells. The cells release a cocktail of therapeutic proteins in response to inflammation, ischemia, hematological disorders, and radiation damage. PLX cell products are grown using the Company's proprietary three-dimensional expansion technology. They are off-the-shelf, requiring no tissue matching prior to administration.

Pluristem has a strong intellectual property position; Company-owned and operated, GMP-certified manufacturing and research facilities; strategic relationships with major research institutions; and a seasoned management team.

### **Safe Harbor Statement**

This press release contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995 and federal securities laws. For example, we are using forward-looking statements when we discuss the findings of the study, the evidence they provide and their potential implications, such as the superiority of placenta-derived

cells over those sourced from fat tissue and bone marrow and the potential power of placental cells to address complex diseases without harming the patient, and when we discuss our plans to advance into clinical studies of PLX-PAD cells in treating preeclampsia. These forward-looking statements and their implications are based on the current expectations of the management of Pluristem only, and are subject to a number of factors and uncertainties that could cause actual results to differ materially from those described in the forward-looking statements. The following factors, among others, could cause actual results to differ materially from those described in the forward-looking statements: changes in technology and market requirements; we may encounter delays or obstacles in launching and/or successfully completing our clinical trials; our products may not be approved by regulatory agencies, our technology may not be validated as we progress further and our methods may not be accepted by the scientific community; we may be unable to retain or attract key employees whose knowledge is essential to the development of our products; unforeseen scientific difficulties may develop with our process; our products may wind up being more expensive than we anticipate; results in the laboratory may not translate to equally good results in real clinical settings; results of preclinical studies may not correlate with the results of human clinical trials; our patents may not be sufficient; our products may harm recipients; changes in legislation; inability to timely develop and introduce new technologies, products and applications; loss of market share and pressure on pricing resulting from competition, which could cause the actual results or performance of Pluristem to differ materially from those contemplated in such forward-looking statements. Except as otherwise required by law, Pluristem undertakes no obligation to publicly release any revisions to these forward-looking statements to reflect events or circumstances after the date hereof or to reflect the occurrence of unanticipated events. For a more detailed description of the risks and uncertainties affecting Pluristem, reference is made to Pluristem's reports filed from time to time with the Securities and Exchange Commission. Except as otherwise required by law, Pluristem undertakes no obligation to publicly release any revisions to these forward-looking statements to reflect events or circumstances after the date hereof or to reflect the occurrence of unanticipated events. For a more detailed description of the risks and uncertainties affecting Pluristem, reference is made to Pluristem's reports filed from time to time with the Securities and Exchange Commission.